Lung Protective Ventilation
Putting All the Evidence Together

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Twenty Years of Clinical Trials
What Can Physicians Do to Stop VILI?

Can the Results Be Explained?

Only Three Positive Trials...
Reducing Tidal Volume Improves Mortality

For the Individual, VT Parallels Driving Pressure

ARDSnet ARMA Trial
Well Selected Patients Benefit From Prone Position

Early, Severe, & Recruitable

Guerin PROSEVA NEJM 2013

Cumulative Probability of Survival

Days

0.0 0.2 0.4 0.6 0.8 1.0

P<0.001

No. at Risk

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<th>0</th>
<th>10</th>
<th>20</th>
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Early Muscle Relaxants May Help

Why?

Papazian NEJM 2010

Figure 2. Probability of Survival through Day 90, According to Study Group.
Clinical Trials in Critical Care
What Have We *Really* Learned?

- **Precise definitions** are needed before an RCT can be usefully translated into practice.

- **Complexity** of critical illness and variation of practice environments render RCTs difficult to execute and limit their relevance to bedside management.

- RCTs are a potentially **dangerous methodology** when misapplied or misinterpreted.
  - Most questions cannot or should not be “trialed.”
Often Violated Rational Sequence

1) Observation
2) Understanding the mechanism(s)
3) Generating the hypothesis
4) Performing the experiments (RCT)

Physiological lessons inform steps 2 and 3.
VILI—The Mechanical Factors

Trans-Pulmonary Pressure
PEEP
Tidal Volume
Plateau

FLOW??
Stress & Strain
Definitions & Measures

- **Stress** — Applied Force > Relaxed Baseline

  “TENSION” Paw – Ppl

- **Strain** — Resulting Elongation Ratio

  “LENGTH” \( \frac{(V_T + PEEP \times C)}{FRC} \)
Mechanisms of Airspace Injury

What Damages Most?

Expanding Alveolus

“Stretch”

Unyielding Collapsed Alveolus

“Shear”

Cyclic Airway Trauma
Dependent VILI Injury (Supine Position)
Which Pressure Best Reflects Tissue Stress?

Alveolar Pressure

Trans-Pulmonary Driving Pressure

PEEP

Less Driving Pressure
Shorter Lever Arm

Fewer Units at Risk
Is a Given Airway DP Safe (or Not) at Every PEEP?
Is a Given DP Safe (or Not) at Every PEEP?
Is a Given DP Safe (or Not) at Every PEEP?

It may depend on $V_E$, position, recruitability, etc.
High Plateau & *Calculated* Strain

\[
\frac{(V_T + [PEEP \times C])}{FRC}
\]

*V_T* Normal

FRC Low

**Normal True Driving Pressure**
IAH increases *Calculated Driving Pressure*

**Graph:**

- **Y-axis:** Plateau airway pressure ($P_{\text{PLAT}}$) cmH$_2$O
- **X-axis:** Intra-abdominal pressure (IAP) cmH$_2$O

**Equations:**
- For $P_{\text{PLAT}}^{10}$: $y = 0.51x + 14.5$, $R^2 = 0.97$
- For $P_{\text{PLAT}}^1$: $y = 0.54x + 9.6$, $R^2 = 0.99$

**Lines:**
- $P_{\text{PLAT}}^{10}$
- $P_{\text{PLAT}}^1$
- $P_{\text{EEP}}^{10}$
- $P_{\text{EEP}}^1$

**Annotations:**
- $DP_{10}$
- $DP_1$
Airway and Transpulmonary Driving Pressures Can Be Very Different

Cortes/ Marini Crit Care Med 2015
Global vs. *Cellular* Stress and Strain

- Both Stress and Strain are important to VILI risk.

- **Cellular Stress** is *tension* that only loosely relates to peak trans-alveolar and driving pressures.

- **Cellular Strain** is *deformation* loosely related to \((VT + PEEP \cdot C) / FRC\).

- The *Product* of Stress and Strain is *Work*
Is VILI Caused By \textit{Unrecovered Work} During the Inflation Cycle?

“Strain”

“Stress”

Length

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<th>Pressure (cm/H\textsubscript{2}O)</th>
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Volume (mL)
```

Tension
Trans-Pulmonary Energy Load Threshold

Joules / Minute

Cressoni, Gattinoni (in press)
Roles for Frequency, Pressure Profile, Flow & I:E Ratio in VILI
**Flow Damage to the Baby Lung?**

For *Any* Given Minute Ventilation

- >3 times *effective* Stretch
- >3 times the *Air Flow*

???????
Faster Flows and Strain Rates Accentuate Hysteresis...

Cressoni, Gattinoni (in press)
Higher Flow Rates Amplify $\Delta P_{dyn}$... ...and Stretching Forces?
Edema Relates to Visco-elastance & Energy Hysteresis

Cressoni, Gattinoni (in press)
Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Marcelo B.P. Amato, M.D., Maureen O. Meade, M.D., Arthur S. Slutsky, M.D.,

Figure 2. Relative Risk of Death in the Hospital versus ΔP in the Combined Cohort after Multivariate Adjustment.

The combined cohort trial included patients who received either a ΔP of 6.0 (5.9–7.5) cm of water or 8.0 (5.7–12.1) cm of water.
Driving Pressure Definitions

- $P_{PLAT} - PEEP$
  \[ P_{PLAT} = (PEEP + Auto-PEEP) \]
- Ratio of tidal volume to compliance ($V_T/C$)
  
  *Respiratory system* compliance

  *Lung compliance*

  *Regional* DP’s vary
The Application of Esophageal Pressure Measurement in Patients with Respiratory Failure

Airway Pressure Targets Do Not Assure Safe Trans-Pulmonary Pressures

Brochard & Colleagues
Vigorous Breathing Violates Objectives of Lung Protection

Consider BOTH phases of the cycle!
High Driving Pressures Occur Normally Occur During Vigorous Exercise

Normal Subjects on Treadmill

42 +/- 16 cmH2O

(CHEST 1997; 112:829-32)
Regional Stress Focusing

Zone of over-distension

Zone of atelectasis
Stress is amplified in high stiffness zones

Can *Airway* Driving Pressure Alone Predict VILI Risk?

- **Better predictor than** $V_T$ or $P_{Plateau}$ **alone**
- **Is not the only contributor to VILI**
  - Sustained strain
  - Amplified junctional forces
  - Tidal opening & closure
  - Frequency & minute ventilation
  - Inspiratory flow and flow profile
  - *Vascular* pressures & flows

- **May overestimate risk**
  - Stiff chest wall
  - Unmeasured auto-PEEP
  - APRV

- **May underestimate risk**
  - Spontaneous breathing efforts
Importance of Flow to VILI … *Two* Components

- **Minute Ventilation**
  - Cumulative *Volume Over Time*
    - *Determines Average Inspiratory Flow* -- $V_E/T_i$
    - Higher $V_E$ → Faster Insp Flow or longer I:E Ratio

- **Mean Inspiratory Flow and Flow Profile**
  - Settings
    - Flow (ACV)
    - Driving Pressure and I:E ratio (PCV)
  - Waveform
Effect of High Peak Insp Flow

Maeda Anesthesiology 2004
Low Pressure Control

High Pressure Normal Rate

High Pressure Extended I:E

High Pressure Short I:E Ratio

High Pressure Low Insp. Flow

Rich, *J. Trauma*, 2000
Lower Frequency & Minute Ventilation Reduce VILI

Frequency and Vascular Pressure Worsen Lung Injury

Frequency and Vascular Pressure

- Normal frequency, normal vascular pressure
- Normal frequency, high vascular pressure

Hemorrhage Score

- F20P20
- F3P35
- F20P35

* indicates significant difference
How Might We Modify *Specific* Flow Through The Baby Lung?

- Decrease the Driving Pressure (PCV)
- Alter the Flow Profile (ACV)
- Adjust the Flow Amplitude (I:E Ratio)
- **Reduce the Minute Ventilation Need**
  - Sedation / Paralysis
  - Fever reduction
  - *Extrapulmonary CO₂ Elimination*
    - Nova Lung, ILA, TGI
  - **Gradual Adaptation**
    - Relax expectations for arterial blood composition
VILI—The *Mechanical* Factors

- Trans-Pulmonary Pressure
- PEEP
- Plateau
- Tidal Volume
- Energy
- Strain
- Driving Pressure

FLOW !!!
Now, A Different Perspective On VILI...
Is Excessive Stress & Strain Only the Pre-condition?

Tissue Over-Stretch

Background Conditions
Conditionally Important to VILI During High Stress / Strain Ventilation

- Position
- PaCO₂ and pH
- FiO₂
- Vascular Pressures
- Temperature
- Minute Ventilation
- Frequency
- Cycle Shaping Contours
  - dP/dt (Inspiratory Flow)
  - I:E (Adverse Tension-Time Product)

Off-Radar (Stealth) Factors??
Body Temperature Affects VILI Expression

Suzuki
_Crit Care Med_
2004

Edema

Hemorrhage
Synchronous Heating

Suzuki
Crit Care Med
2004
The Baby Lung of ARDS Has A Lot of Work to Perform!

For *Any* Given Minute Ventilation

- **Multiples** of *Stretch*
- **Multiples** of *Gas flow*
- Less than Proportional *Blood Flows*
Without Help, the Healthy Lung Fails at Volumes < 20%
Only The Hyper-Ventilators Experienced Lung Injury

Mascheroni, Kolobow 1988
Lung Overstretch and Recruitment of *Underperfused* Units (?) Increase VD/VT

Paradoxical Response To PEEP & Mean Paw
The *Real* Cause of ARDS Dead Space
Does the *aerated* ARDS dead space adversely affect *alveolar* pH?

\[ \text{PACO}_2 < \text{PaCO}_2 \]

Unyielding Collapsed Alveolus

Shunted CO\(_2\)
Effect of inhaled CO₂ on hemorrhagic consolidation due to unilateral pulmonary arterial ligation

L. HENRY EDMUNDS, JR. AND JESS C. HOLM
Division of Surgery and Urology, Board of Leyden, Harvard

FIG. 1. Inflated left lungs of animals from group C-5 (left) and group CO₂-5 (right). Left lung of the CO₂-treated animal had only small peripheral areas of hemorrhagic consolidation.
Eucapnic VILI
Hypercapnic VILI
Conditional Benefit of Hypercapnia

Kregenow, Crit Care Med 2006
Regional High PEEP-like Effect
Sustained Traction of “Supine Dependent” Units
Homogeneous Transpulmonary Pressures
Proning Benefits Severe, Early, Recruitable ARDS
Lower Frequency & Minute Ventilation Reduce VILI
Vascular Pressure Gradient
Vascular Flow May Be An Important VILI Co-Factor

- Energy Dissipation
- Vascular Interdependence
- Endothelial Shear

Reducing Oxygen Demand and Ventilation Targets May Lower the Risk For VILI

Hotchkiss, Broccard
The Baby Lung of ARDS

For *Any* Given Minute Ventilation

- >3 times the *Stretch*  
- >3 times the *Gas flow*

- >2 times the *Blood Flow*

Do Not Forget *Vascular* Flows!
Potential Importance of Oxygen Demand on VILI Expression

- Ventilation Requirement
  - Ventilation Pressures and Cycling Frequency
  - Energy Delivery
- Cardiac Output
  - Pulmonary Blood Flow
  - Microvascular Pressure Gradient
Vigorous Breathing Violates Objectives of Lung Protection

Consider Paralytics in the Early Phase
Early Muscle Relaxants May Help

Why?

Papazian NEJM 2010
Ideal Physiologic Response to ARDS

- Rescue
- Stabilization
- Re-loading
- Recovery
By Taking *Early* Control Do We Interrupt A Catastrophic Feedback Sequence?
Thank You